GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION

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April 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Guidance for Industry on Variations in Drug Products That May Be Included in a Single Abbreviated New Drug Application [Docket No. 98D-1268].

Dear Sir/Madam:

On behalf of the Science Committee of the Generic Pharmaceutical Industry Association (GPIA), I am forwarding comments from some of our member companies on "Guidance for Industry on Variations in Drug Products That May Be Included in a Single Abbreviated New Drug Application", 64 FR 4117, January 27, 1999.

GPIA is comprised of the manufacturers and distributors of generic medicines (as well as the providers of technical services and goods to these firms). Many of our members will be directly impacted by implementation of the subject level 1 guidance, which was effective immediately upon its publication in the *Federal Register.*

Comments received from GPIA members are as follows:

Section II.A.

Variations in formulations should generally be allowed in a single ANDA, regardless of the number of corresponding NDAs. Further, separate NDAs for different clinical indications should have no impact on the number of ANDAs required for different dosage forms.

Section II.B.

First bullet:

Reference is made only to capsules. What about tablets? [Section III which is referred to for more specific guidance does not address capsules, *per se.*] Also how is the term "differences" (in formulations) defined?

98D-1268

C2

If variations in the formulations for the reference listed drug are allowed in the same NDA, the generic product should also be allowed to have such variations in a single ANDA. In addition the number of biostudies required to prove bioequivalence of the drug products should not be the deciding factor for single or separate ANDAs.

Second bullet:

Section 21 CFR 320.22(d)(4) addresses a reformulated drug product by an *already* approved manufacturer. This does not apply to an original ANDA. Section 21 CFR 320.22(d)(2) appears to be a more appropriate citation.

It has been the FDA's practice to allow qualification of a different tablet shape through comparative dissolution profiles (alluded to in the MAPP 5223.2). Requiring separate BE studies for different shapes, as appears to be the implication here, would, therefore, represent an *increase* in regulatory burden and bump this guidance out of the level 1 category.

Section II.C.

It is agreed that multiple biostudies would need to be performed to assure equivalence to the reference listed drug product, but these could be contained in the same application if the reference listed drug has only on application for different dosage forms.

Section II.E.

Strengths and volumes for pharmacy bulk packages that can share a single ANDA should not be restricted to the packages contained within the reference listed drug application. Rather, the Agency should set some kind of lower limit on acceptable package size, applicable to both ANDAs and NDAs. There should be no upper limit.

Section II.F.

Section IV is referred to for additional guidance. There is no Section IV in the subject guidance.

Section II.G.

This section should be eliminated. Current ANDAs contain methods to demonstrate manufacturability and stability. Separate applications should not be required based on packaging configurations. This will inhibit innovation in packaging to enhance stability, patient compliance, etc. Such a requirement does not appear to exist for NDAs.

It is agreed that, in general, different packaging formats in which the drug delivery device is integral to the use of the product usually should be submitted as separate applications. However, for parenteral products where the packaging of the solution into vials or syringes is performed, separate applications should not be necessary. Such applications would differ only in packaging components, the filling section, and the stability reports. All other areas of the applications would be redundant.

Section III.A.

The table appears to be based on "ease of review" only. For example, for multiple strengths of a single formulation (i.e., exact multiples), multiple colors alone would require separate ANDAs. However, for a single strength, multiple colors can be included in a single ANDA. [When would the latter case hold?] The former case is often desirable for medication error prevention, yet separate ANDAs provides a disincentive to use different colors for different strengths.

Section III.B.

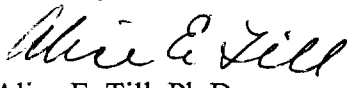
It is not agreed that separate applications should be submitted for preserved and nonpreserved parenteral products. If separate NDAs have not been submitted for the corresponding reference listed products, neither should separate ANDAs be required.

Section III.C.

Requirements for separate or single ANDAs based on method of manufacture of transdermals should be consistent with those for NDAs.

Thank you for the opportunity to submit our comments on the subject guidance. We would appreciate your consideration of appropriate revisions to the guidance based on these comments.

Sincerely,



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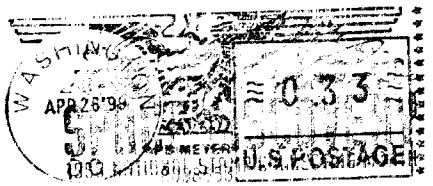

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